

NCIVISION: A Siamese Neural Network for Molecular Similarity Prediction MEP and RDG Images

Rafael Campos Vieira,[†] Érica C. M. Nascimento,[‡] Letícia A. Nascimento,[†]
Arthur Alves Nascimento,[‡] Nicolas Ricardo de Melo Alves,[‡] and João B. L.
Martins*,^{†,‡}

[†]*Department of Pharmacy, Faculty of Health Sciences, University of Brasília, Brasília,
Brazil*

[‡]*Institute of Chemistry, University of Brasília, Brasília, Brazil*

E-mail: lopes@unb.br

Phone: +556131073886

Supporting Information Available

Table S1: Tanimoto similarity values S_T calculated with RDKit for TKI molecules.

molecule	poma	PF-114	7a	7b	7c	7d	7e	7f	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k
poma	1.0	0.679	0.725	0.688	0.659	0.644	0.667	0.651	0.663	0.712	0.706	0.728	0.728	0.694	0.651	0.636	0.644	0.667	0.651	0.484	0.25	0.255	0.257	0.28	0.34	0.404	0.195	0.198	0.2	0.221	
PF-114	0.679	1.0	0.688	0.692	0.643	0.628	0.651	0.635	0.667	0.696	0.684	0.651	0.651	0.621	0.58	0.58	0.567	0.573	0.615	0.635	0.286	0.269	0.274	0.276	0.264	0.17	0.225	0.211	0.214	0.216	0.205
7a	0.725	0.688	1.0	0.843	0.753	0.734	0.763	0.722	0.737	0.747	0.733	0.696	0.696	0.663	0.619	0.619	0.605	0.612	0.718	0.679	0.307	0.264	0.269	0.272	0.31	0.185	0.243	0.205	0.209	0.211	0.245
7b	0.688	0.692	0.843	1.0	0.784	0.763	0.795	0.797	0.767	0.778	0.764	0.724	0.724	0.688	0.642	0.642	0.627	0.634	0.747	0.705	0.277	0.272	0.277	0.28	0.347	0.157	0.215	0.211	0.215	0.217	0.277
7c	0.659	0.643	0.753	0.784	1.0	0.867	0.803	0.738	0.688	0.696	0.727	0.691	0.691	0.659	0.616	0.616	0.602	0.628	0.712	0.738	0.274	0.28	0.286	0.288	0.327	0.159	0.214	0.221	0.225	0.227	0.262
7d	0.644	0.628	0.734	0.763	0.867	1.0	0.782	0.72	0.671	0.679	0.709	0.675	0.675	0.644	0.602	0.602	0.589	0.614	0.695	0.659	0.269	0.275	0.28	0.283	0.32	0.157	0.211	0.217	0.221	0.223	0.257
7e	0.667	0.651	0.763	0.795	0.803	0.782	1.0	0.747	0.696	0.705	0.737	0.766	0.7	0.667	0.683	0.624	0.667	0.675	0.744	0.683	0.276	0.259	0.264	0.267	0.303	0.161	0.216	0.202	0.205	0.207	0.264
7f	0.651	0.635	0.722	0.797	0.738	0.72	0.747	1.0	0.679	0.688	0.718	0.683	0.683	0.651	0.609	0.609	0.596	0.602	0.704	0.667	0.271	0.314	0.333	0.262	0.484	0.158	0.212	0.252	0.269	0.204	0.402
7g	0.663	0.667	0.737	0.767	0.688	0.671	0.696	0.679	1.0	0.747	0.733	0.696	0.696	0.663	0.619	0.619	0.605	0.612	0.696	0.7	0.282	0.276	0.282	0.284	0.297	0.164	0.22	0.216	0.22	0.234	0.234
7h	0.712	0.696	0.747	0.778	0.696	0.679	0.705	0.688	0.747	1.0	0.792	0.75	0.75	0.712	0.667	0.667	0.651	0.659	0.705	0.688	0.297	0.267	0.272	0.275	0.287	0.187	0.234	0.207	0.211	0.213	0.224
7i	0.766	0.684	0.733	0.764	0.727	0.709	0.737	0.718	0.733	0.792	1.0	0.833	0.833	0.789	0.74	0.74	0.722	0.731	0.737	0.718	0.327	0.269	0.275	0.29	0.303	0.2	0.26	0.209	0.213	0.226	0.238
7j	0.728	0.651	0.696	0.724	0.691	0.675	0.766	0.683	0.696	0.75	0.833	1.0	0.863	0.818	0.89	0.769	0.867	0.878	0.744	0.704	0.314	0.259	0.264	0.279	0.291	0.193	0.25	0.202	0.205	0.218	0.229
7k	0.728	0.651	0.696	0.724	0.691	0.675	0.7	0.683	0.696	0.75	0.833	0.863	1.0	0.842	0.769	0.89	0.75	0.759	0.7	0.683	0.314	0.259	0.264	0.279	0.291	0.193	0.25	0.202	0.205	0.218	0.229
8f	0.694	0.621	0.663	0.688	0.659	0.644	0.667	0.651	0.663	0.712	0.789	0.818	0.842	1.0	0.775	0.797	0.714	0.723	0.687	0.651	0.302	0.25	0.255	0.269	0.28	0.186	0.241	0.195	0.198	0.211	0.221
8g	0.651	0.58	0.619	0.642	0.616	0.602	0.683	0.609	0.619	0.667	0.74	0.89	0.769	0.775	1.0	0.867	0.868	0.855	0.663	0.628	0.271	0.221	0.225	0.239	0.25	0.2	0.212	0.168	0.171	0.183	0.193
8h	0.651	0.58	0.619	0.642	0.616	0.602	0.624	0.609	0.619	0.667	0.74	0.769	0.89	0.797	0.867	1.0	0.753	0.741	0.624	0.609	0.271	0.221	0.225	0.239	0.25	0.2	0.212	0.168	0.171	0.183	0.193
8i	0.636	0.567	0.605	0.627	0.602	0.589	0.667	0.596	0.605	0.651	0.722	0.867	0.75	0.714	0.868	0.753	1.0	0.833	0.647	0.614	0.266	0.217	0.221	0.234	0.245	0.186	0.209	0.165	0.168	0.179	0.19
8j	0.644	0.573	0.612	0.634	0.628	0.614	0.675	0.602	0.612	0.659	0.731	0.878	0.759	0.723	0.855	0.741	0.833	1.0	0.655	0.621	0.269	0.219	0.223	0.236	0.248	0.188	0.211	0.167	0.169	0.181	0.191
8k	0.667	0.651	0.718	0.747	0.712	0.695	0.744	0.704	0.696	0.705	0.737	0.744	0.7	0.687	0.663	0.624	0.647	0.655	1.0	0.816	0.276	0.259	0.264	0.267	0.304	0.161	0.216	0.202	0.205	0.207	0.241
8l	0.651	0.635	0.679	0.705	0.738	0.659	0.683	0.667	0.7	0.688	0.718	0.704	0.683	0.651	0.628	0.609	0.614	0.621	0.816	1.0	0.271	0.255	0.259	0.262	0.286	0.158	0.212	0.198	0.202	0.204	0.225
2a	0.484	0.286	0.307	0.277	0.274	0.269	0.276	0.271	0.282	0.297	0.327	0.314	0.314	0.302	0.271	0.271	0.266	0.269	0.276	0.271	1.0	0.489	0.571	0.578	0.617	0.641	0.847	0.406	0.478	0.483	0.515
2b	0.25	0.209	0.264	0.272	0.28	0.275	0.259	0.314	0.276	0.267	0.269	0.259	0.259	0.25	0.221	0.221	0.217	0.219	0.259	0.255	0.489	1.0	0.836	0.705	0.602	0.287	0.406	0.851	0.709	0.595	0.506
2c	0.257	0.274	0.269	0.277	0.286	0.28	0.264	0.333	0.282	0.272	0.275	0.264	0.254	0.255	0.225	0.225	0.221	0.223	0.264	0.259	0.333	0.836	1.0	0.795	0.724	0.333	0.478	0.709	0.847	0.671	0.61
2d	0.257	0.276	0.272	0.28	0.288	0.283	0.267	0.262	0.284	0.275	0.29	0.279	0.279	0.269	0.239	0.239	0.234	0.236	0.267	0.262	0.578	0.705	0.795	1.0	0.605	0.337	0.483	0.595	0.671	0.845	0.506
2e	0.28	0.264	0.31	0.347	0.327	0.32	0.33	0.484	0.297	0.287	0.303	0.291	0.291	0.28	0.25	0.25	0.245	0.248	0.304	0.286	0.617	0.602	0.724	0.605	1.0	0.366	0.517	0.506	0.61	0.506	0.845
2f	0.34	0.17	0.185	0.157	0.159	0.157	0.161	0.158	0.164	0.187	0.2	0.193	0.193	0.186	0.2	0.2	0.186	0.188	0.161	0.158	0.641	0.287	0.333	0.337	0.366	1.0	0.536	0.224	0.265	0.267	0.293
2g	0.404	0.225	0.243	0.215	0.214	0.211	0.216	0.212	0.22	0.234	0.26	0.25	0.25	0.241	0.212	0.212	0.209	0.211	0.216	0.212	0.847	0.406	0.478	0.483	0.517	0.536	1.0	0.495	0.576	0.583	0.622
2h	0.195	0.21	0.205	0.211	0.211	0.217	0.202	0.252	0.216	0.207	0.209	0.202	0.202	0.195	0.168	0.168	0.165	0.167	0.202	0.198	0.406	0.851	0.709	0.595	0.506	0.224	0.495	1.0	0.838	0.709	0.607
2i	0.214	0.214	0.209	0.215	0.225	0.221	0.205	0.269	0.22	0.211	0.213	0.205	0.205	0.198	0.171	0.171	0.168	0.169	0.205	0.202	0.478	0.709	0.847	0.671	0.61	0.265	0.576	0.838	1.0	0.797	0.727
2j	0.200	0.216	0.211	0.217	0.227	0.223	0.207	0.204	0.222	0.213	0.226	0.218	0.218	0.211	0.183	0.183	0.179	0.181	0.207	0.204	0.483	0.595	0.671	0.845	0.506	0.267	0.583	0.709	0.797	1.0	0.61
2k	0.221	0.205	0.245	0.277	0.262	0.257	0.264	0.402	0.234	0.224	0.238	0.229	0.229	0.221	0.193	0.193	0.19	0.191	0.241	0.225	0.517	0.506	0.61	0.506	0.845	0.293	0.622	0.607	0.727	0.61	1.0

Table S2: Inverse distance values d^{-1} calculated by the model for the TKI molecules.

MOLECULE	poma	PF-114	7a	7b	7c	7d	7e	7f	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	
poma	1.0	0.826	0.786	0.748	0.611	0.791	0.547	0.573	0.925	0.79	0.741	0.671	0.725	0.747	0.692	0.631	0.631	0.774	0.682	0.929	0.861	0.727	0.971	0.813	0.828	0.94	0.907	0.928	0.852	0.978		
PF-114	0.826	1.0	0.942	0.888	0.701	0.949	0.618	0.652	0.885	0.947	0.878	0.781	0.856	0.886	0.81	0.728	0.728	0.924	0.796	0.777	0.953	0.858	0.847	0.98	0.992	0.871	0.802	0.902	0.776	0.772	0.812	
7a	0.786	0.942	1.0	0.939	0.733	0.991	0.643	0.68	0.839	0.99	0.928	0.821	0.903	0.937	0.852	0.762	0.763	0.979	0.837	0.741	0.9	0.906	0.805	0.959	0.938	0.827	0.764	0.855	0.741	0.691	0.773	
7b	0.748	0.888	0.939	1.0	0.769	0.932	0.67	0.711	0.796	0.933	0.988	0.867	0.959	0.996	0.902	0.801	0.802	0.957	0.886	0.707	0.851	0.962	0.765	0.903	0.884	0.785	0.728	0.81	0.707	0.662	0.737	
7c	0.611	0.701	0.733	0.769	1.0	0.728	0.839	0.903	0.643	0.729	0.777	0.772	0.795	0.771	0.839	0.95	0.949	0.744	0.854	0.584	0.678	0.793	0.622	0.711	0.699	0.635	0.598	0.652	0.584	0.552	0.603	
7d	0.791	0.949	0.991	0.932	0.728	1.0	0.639	0.676	0.845	0.992	0.921	0.815	0.896	0.93	0.846	0.757	0.758	0.972	0.832	0.746	0.907	0.899	0.81	0.967	0.945	0.832	0.769	0.861	0.746	0.695	0.778	
7e	0.547	0.618	0.701	0.733	0.611	0.949	1.0	0.922	0.925	0.992	0.922	0.815	0.896	0.93	0.846	0.757	0.758	0.972	0.832	0.746	0.907	0.899	0.81	0.967	0.945	0.832	0.769	0.861	0.746	0.695	0.778	
7f	0.573	0.652	0.68	0.711	0.903	0.676	0.722	1.0	0.601	0.677	0.717	0.798	0.733	0.712	0.77	0.863	0.862	0.889	0.783	0.549	0.632	0.731	0.583	0.661	0.651	0.595	0.562	0.609	0.549	0.522	0.567	
7g	0.925	0.885	0.839	0.796	0.643	0.854	0.572	0.601	1.0	0.844	0.788	0.709	0.77	0.795	0.733	0.665	0.665	0.825	0.722	0.864	0.925	0.772	0.951	0.87	0.888	0.98	0.895	0.979	0.863	0.797	0.908	
8a	0.79	0.947	0.99	0.933	0.729	0.992	0.64	0.677	0.844	1.0	0.923	0.816	0.898	0.932	0.848	0.758	0.759	0.974	0.833	0.745	0.905	0.9	0.809	0.963	0.942	0.831	0.768	0.859	0.744	0.694	0.788	
8b	0.741	0.878	0.928	0.988	0.721	0.921	0.676	0.717	0.788	0.923	1.0	0.876	0.971	0.99	0.912	0.809	0.81	0.946	0.805	0.701	0.842	0.973	0.758	0.893	0.875	0.777	0.722	0.802	0.701	0.656	0.73	
8c	0.671	0.818	0.881	0.867	0.872	0.815	0.747	0.708	0.709	0.816	0.876	1.0	0.9	0.9	0.868	0.957	0.914	0.915	0.835	0.976	0.638	0.752	0.897	0.848	0.793	0.779	0.7	0.655	0.72	0.638	0.601	
8e	0.725	0.856	0.903	0.959	0.795	0.896	0.69	0.733	0.77	0.898	0.971	0.9	1.0	0.961	0.938	0.83	0.83	0.92	0.92	0.987	0.821	0.989	0.741	0.87	0.852	0.759	0.766	0.783	0.687	0.644	0.714	
8f	0.692	0.886	0.933	0.988	0.815	0.911	0.677	0.717	0.788	0.891	0.971	0.968	0.971	1.0	0.968	0.938	0.83	0.83	0.92	0.92	0.987	0.821	0.989	0.741	0.87	0.852	0.759	0.766	0.783	0.687	0.644	
8g	0.692	0.81	0.852	0.902	0.839	0.84	0.728	0.77	0.733	0.848	0.912	0.957	0.908	0.94	1.0	0.958	0.978	0.967	0.979	0.657	0.777	0.934	0.706	0.823	0.807	0.707	0.675	0.745	0.657	0.617	0.684	
8h	0.631	0.728	0.762	0.801	0.59	0.757	0.804	0.863	0.665	0.758	0.809	0.914	0.83	0.803	0.878	1.0	0.998	0.774	0.894	0.602	0.703	0.827	0.643	0.738	0.726	0.657	0.617	0.672	0.602	0.569	0.623	
8i	0.631	0.728	0.762	0.802	0.59	0.757	0.804	0.862	0.665	0.759	0.81	0.915	0.83	0.804	0.879	0.998	1.0	0.775	0.805	0.602	0.703	0.828	0.643	0.738	0.726	0.658	0.617	0.675	0.602	0.569	0.623	
8j	0.774	0.924	0.979	0.957	0.744	0.972	0.651	0.689	0.825	0.943	0.946	0.835	0.92	0.955	0.879	0.744	0.775	1.0	0.852	0.73	0.884	0.922	0.792	0.904	0.92	0.813	0.752	0.84	0.73	0.682	0.714	
8k	0.682	0.796	0.837	0.886	0.854	0.832	0.734	0.683	0.728	0.833	0.895	0.976	0.92	0.887	0.969	0.894	0.895	0.852	1.0	0.648	0.766	0.917	0.696	0.809	0.794	0.712	0.666	0.733	0.648	0.61	0.673	
8l	0.929	0.777	0.741	0.707	0.574	0.746	0.525	0.549	0.864	0.745	0.701	0.638	0.687	0.687	0.687	0.602	0.602	0.602	0.602	1.0	0.807	0.688	0.904	0.765	0.779	0.877	0.976	0.848	0.993	0.846	0.907	
2a	0.861	0.953	0.931	0.953	0.678	0.907	0.6	0.632	0.725	0.824	0.922	0.752	0.821	0.909	0.759	0.703	0.703	0.703	0.703	0.703	1.0	0.624	0.883	0.936	0.957	0.97	0.935	0.844	0.971	0.846	0.907	
2b	0.807	0.853	0.898	0.902	0.639	0.874	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.772	0.624	1.0	0.883	0.936	0.957	0.97	0.935	0.844	0.971	0.846	0.907	
2c	0.971	0.847	0.805	0.765	0.622	0.81	0.556	0.583	0.951	0.809	0.758	0.684	0.741	0.763	0.706	0.643	0.643	0.643	0.643	0.643	0.792	0.696	0.904	0.883	0.743	1.0	0.833	0.849	0.967	0.938	0.924	0.831
2d	0.813	0.98	0.959	0.903	0.711	0.967	0.626	0.661	0.87	0.963	0.983	0.793	0.87	0.901	0.823	0.738	0.739	0.739	0.739	0.739	0.809	0.765	0.936	0.933	0.833	1.0	0.977	0.856	0.79	0.886	0.765	0.712
2e	0.828	0.992	0.938	0.884	0.699	0.945	0.617	0.651	0.888	0.942	0.875	0.779	0.852	0.882	0.807	0.726	0.726	0.726	0.726	0.726	0.920	0.794	0.779	0.957	0.855	0.849	0.977	1.0	0.874	0.805	0.979	0.724
2f	0.94	0.871	0.827	0.785	0.635	0.832	0.566	0.595	0.98	0.831	0.777	0.7	0.759	0.783	0.723	0.657	0.658	0.658	0.658	0.658	0.813	0.712	0.877	0.91	0.762	0.967	0.856	0.874	1.0	0.91	0.961	0.877
2g	0.64	0.802	0.764	0.728	0.598	0.769	0.536	0.562	0.895	0.768	0.722	0.655	0.706	0.727	0.675	0.617	0.617	0.617	0.617	0.617	0.732	0.666	0.936	0.835	0.708	0.938	0.79	0.805	0.91	1.0	0.878	0.961
2h	0.907	0.902	0.855	0.81	0.652	0.861	0.579	0.609	0.979	0.859	0.802	0.72	0.783	0.808	0.765	0.675	0.675	0.675	0.675	0.675	0.84	0.733	0.848	0.944	0.785	0.902	0.886	0.905	0.961	0.878	1.0	0.848
2i	0.776	0.776	0.741	0.741	0.611	0.776	0.547	0.573	0.925	0.79	0.741	0.671	0.725	0.747	0.692	0.631	0.631	0.774	0.682	0.929	0.861	0.727	0.971	0.813	0.828	0.94	0.907	0.928	0.852	0.978	1.0	0.848
2j	0.722	0.852	0.691	0.662	0.552	0.695	0.495	0.522	0.797	0.694	0.656	0.601	0.644	0.661	0.617	0.569	0.569	0.569	0.569	0.569	0.682	0.66	0.911	0.749	0.645	0.831	0.712	0.724	0.808	0.879	0.783	0.911
2k	0.978	0.812	0.773	0.737	0.603	0.778	0.541	0.567	0.908	0.777	0.73	0.662	0.714	0.735	0.682	0.623	0.623	0.623	0.623	0.623	0.673	0.649	0.952	0.799	0.815	0.923	0.984	0.918	0.946	0.867	1.0	0.848

Table S3: Tanimoto similarity values S_T calculated with RDKit for candidate AChEI molecules.

MOLECULE	DNP	3AD	3AS	3CD	3CS	3ED	3ES	3HD	3HS	3SD	3SS	5AD	5AS	5CD	5CS	5ED	5ES	5HD	5HS	5SD	5SS	SAD	SAS	SCD	SCS	SED	SES	SHD	SHS	SSD	SSS
DNP	1.0	0.117	0.131	0.121	0.135	0.121	0.135	0.125	0.14	0.129	0.143	0.113	0.127	0.117	0.131	0.118	0.133	0.124	0.137	0.125	0.139	0.108	0.101	0.111	0.104	0.12	0.104	0.115	0.108	0.111	0.112
3AD	0.117	1.0	0.757	0.738	0.579	0.638	0.519	0.667	0.539	0.706	0.557	0.889	0.726	0.681	0.557	0.62	0.506	0.657	0.526	0.653	0.537	0.727	0.644	0.521	0.481	0.5	0.427	0.479	0.443	0.461	0.463
3AS	0.131	0.757	1.0	0.579	0.764	0.519	0.671	0.539	0.699	0.557	0.733	0.726	0.9	0.557	0.711	0.506	0.654	0.532	0.68	0.537	0.684	0.635	0.628	0.475	0.459	0.458	0.409	0.438	0.424	0.422	0.443
3CD	0.121	0.738	0.579	1.0	0.746	0.667	0.539	0.698	0.562	0.738	0.579	0.681	0.557	0.883	0.714	0.647	0.526	0.688	0.547	0.681	0.557	0.521	0.481	0.714	0.629	0.521	0.443	0.5	0.461	0.479	0.481
3CS	0.135	0.579	0.764	0.746	1.0	0.539	0.699	0.562	0.729	0.579	0.764	0.557	0.711	0.714	0.896	0.526	0.68	0.554	0.708	0.557	0.711	0.475	0.459	0.62	0.613	0.475	0.424	0.455	0.439	0.438	0.459
3ED	0.121	0.638	0.519	0.667	0.539	1.0	0.746	0.754	0.583	0.738	0.6	0.657	0.519	0.687	0.538	0.931	0.725	0.742	0.568	0.758	0.597	0.461	0.427	0.479	0.443	0.542	0.629	0.522	0.48	0.714	0.5
3ES	0.135	0.519	0.671	0.539	0.699	0.746	1.0	0.583	0.779	0.6	0.764	0.519	0.688	0.538	0.716	0.725	0.938	0.575	0.757	0.597	0.781	0.422	0.409	0.438	0.424	0.494	0.613	0.474	0.457	0.62	0.476
3HD	0.125	0.667	0.539	0.698	0.562	0.754	0.583	1.0	0.734	0.692	0.539	0.687	0.538	0.719	0.56	0.73	0.568	0.944	0.712	0.687	0.538	0.479	0.443	0.5	0.461	0.5	0.48	0.7	0.612	0.522	0.443
3HS	0.14	0.539	0.699	0.562	0.729	0.583	0.779	0.734	1.0	0.56	0.699	0.538	0.716	0.56	0.746	0.568	0.757	0.723	0.935	0.538	0.716	0.438	0.424	0.455	0.439	0.456	0.457	0.603	0.597	0.474	0.424
3SD	0.129	0.706	0.557	0.738	0.579	0.738	0.6	0.692	0.56	1.0	0.757	0.653	0.537	0.681	0.557	0.716	0.584	0.682	0.545	0.889	0.726	0.5	0.463	0.521	0.481	0.727	0.5	0.5	0.462	0.542	0.644
3SS	0.143	0.557	0.733	0.579	0.764	0.6	0.764	0.539	0.699	0.757	1.0	0.537	0.684	0.557	0.711	0.584	0.743	0.532	0.68	0.726	0.9	0.458	0.443	0.475	0.459	0.635	0.476	0.438	0.424	0.494	0.628
5AD	0.113	0.889	0.726	0.681	0.557	0.657	0.519	0.687	0.538	0.653	0.537	1.0	0.767	0.75	0.575	0.662	0.506	0.701	0.544	0.718	0.554	0.671	0.618	0.5	0.463	0.481	0.429	0.48	0.444	0.462	0.447
5AS	0.127	0.726	0.9	0.557	0.711	0.519	0.688	0.538	0.716	0.537	0.684	0.767	1.0	0.575	0.773	0.506	0.692	0.532	0.72	0.554	0.744	0.61	0.585	0.458	0.443	0.442	0.411	0.439	0.425	0.424	0.429
5CD	0.117	0.681	0.557	0.883	0.714	0.687	0.538	0.719	0.56	0.681	0.557	0.75	0.575	1.0	0.757	0.691	0.525	0.734	0.566	0.75	0.575	0.5	0.463	0.657	0.603	0.5	0.444	0.5	0.462	0.48	0.463
5CS	0.131	0.557	0.711	0.714	0.896	0.538	0.716	0.56	0.746	0.557	0.711	0.575	0.773	0.757	1.0	0.525	0.72	0.553	0.75	0.575	0.773	0.458	0.443	0.595	0.57	0.458	0.425	0.456	0.44	0.439	0.443
5ED	0.118	0.62	0.506	0.647	0.526	0.931	0.725	0.73	0.568	0.716	0.584	0.662	0.506	0.691	0.525	1.0	0.754	0.774	0.595	0.761	0.582	0.449	0.417	0.467	0.432	0.527	0.611	0.507	0.468	0.667	0.488
5ES	0.133	0.506	0.654	0.526	0.68	0.725	0.938	0.568	0.757	0.584	0.743	0.506	0.692	0.525	0.72	0.754	1.0	0.581	0.786	0.582	0.784	0.412	0.4	0.427	0.414	0.481	0.577	0.462	0.446	0.603	0.465
5HD	0.124	0.657	0.532	0.688	0.554	0.742	0.575	0.944	0.723	0.682	0.532	0.701	0.532	0.734	0.553	0.774	0.581	1.0	0.754	0.701	0.532	0.473	0.438	0.493	0.455	0.493	0.474	0.661	0.603	0.514	0.438
5HS	0.137	0.526	0.68	0.547	0.708	0.568	0.757	0.712	0.935	0.545	0.68	0.544	0.72	0.566	0.75	0.595	0.786	0.754	1.0	0.544	0.72	0.427	0.414	0.443	0.429	0.444	0.446	0.586	0.56	0.462	0.414
5SD	0.125	0.653	0.537	0.681	0.557	0.758	0.597	0.687	0.538	0.889	0.726	0.718	0.554	0.75	0.575	0.761	0.582	0.701	0.544	1.0	0.767	0.481	0.447	0.5	0.463	0.671	0.5	0.48	0.444	0.541	0.618
5SS	0.139	0.537	0.684	0.557	0.711	0.597	0.781	0.538	0.716	0.726	0.9	0.554	0.744	0.575	0.773	0.582	0.784	0.532	0.72	0.767	1.0	0.442	0.429	0.458	0.443	0.61	0.477	0.439	0.425	0.494	0.585
SAD	0.108	0.727	0.635	0.521	0.475	0.461	0.422	0.479	0.438	0.5	0.458	0.671	0.61	0.5	0.458	0.449	0.412	0.473	0.427	0.481	0.442	1.0	0.71	0.73	0.533	0.697	0.474	0.656	0.493	0.627	0.513
SAS	0.101	0.644	0.628	0.481	0.459	0.427	0.409	0.443	0.424	0.463	0.443	0.618	0.585	0.463	0.443	0.417	0.4	0.438	0.414	0.447	0.429	0.71	1.0	0.533	0.754	0.513	0.658	0.493	0.686	0.474	0.722
SCD	0.111	0.521	0.475	0.714	0.62	0.479	0.438	0.5	0.455	0.521	0.475	0.5	0.458	0.657	0.595	0.467	0.427	0.493	0.443	0.5	0.458	0.73	0.533	1.0	0.697	0.73	0.493	0.689	0.514	0.656	0.533
SCS	0.104	0.481	0.459	0.629	0.613	0.443	0.424	0.461	0.439	0.481	0.459	0.463	0.443	0.603	0.57	0.432	0.414	0.455	0.429	0.463	0.443	0.533	0.754	0.697	1.0	0.533	0.686	0.514	0.716	0.493	0.754
SED	0.12	0.5	0.458	0.521	0.475	0.542	0.494	0.5	0.456	0.727	0.635	0.481	0.442	0.5	0.458	0.527	0.481	0.493	0.444	0.671	0.61	0.697	0.513	0.73	0.533	1.0	0.554	0.683	0.514	0.73	0.71
SES	0.104	0.427	0.409	0.443	0.424	0.629	0.613	0.48	0.457	0.5	0.476	0.429	0.411	0.444	0.425	0.611	0.577	0.474	0.446	0.5	0.477	0.474	0.658	0.493	0.686	0.554	1.0	0.535	0.769	0.697	0.754
SHD	0.115	0.479	0.438	0.5	0.455	0.522	0.474	0.7	0.603	0.5	0.438	0.48	0.439	0.5	0.456	0.507	0.462	0.661	0.586	0.48	0.439	0.656	0.493	0.689	0.514	0.683	0.535	1.0	0.683	0.746	0.493
SHS	0.108	0.443	0.424	0.461	0.439	0.48	0.457	0.612	0.597	0.462	0.424	0.444	0.425	0.462	0.44	0.468	0.446	0.603	0.56	0.444	0.425	0.493	0.686	0.514	0.716	0.514	0.769	0.683	1.0	0.535	0.686
SSD	0.111	0.461	0.422	0.479	0.438	0.714	0.62	0.522	0.474	0.542	0.494	0.462	0.424	0.48	0.439	0.667	0.603	0.514	0.462	0.541	0.494	0.627	0.474	0.656	0.493	0.73	0.697	0.746	0.535	1.0	0.554
SSS	0.112	0.463	0.443	0.481	0.459	0.5	0.476	0.443	0.424	0.644	0.628	0.447	0.429	0.463	0.443	0.488	0.465	0.438	0.414	0.618	0.585	0.513	0.722	0.533	0.754	0.71	0.754	0.493	0.686	0.554	1.0

Table S4: Inverse distance values d^{-1} calculated by the model for candidate AChEI molecules.

MOLECULE	DNP	3AD	3AS	3CD	3CS	3ED	3ES	3HD	3HS	3SD	3SS	5AD	5AS	5CD	5CS	5ED	5ES	5HD	5HS	5SD	5SS	SAD	SAS	SCD	SCS	SED	SES	SHD	SHS	SSD	SSS
DNP	1.0	0.154	0.19	0.179	0.222	0.197	0.258	0.215	0.185	0.177	0.196	0.193	0.182	0.181	0.169	0.186	0.178	0.194	0.221	0.186	0.182	0.195	0.21	0.247	0.296	0.187	0.227	0.185	0.2	0.231	0.21
3AD	0.154	1.0	0.447	0.522	0.336	0.417	0.277	0.352	0.48	0.541	0.42	0.432	0.505	0.507	0.643	0.474	0.534	0.427	0.338	0.474	0.505	0.424	0.368	0.291	0.243	0.466	0.324	0.479	0.403	0.316	0.367
3AS	0.19	0.447	1.0	0.758	0.574	0.858	0.42	0.622	0.867	0.72	0.871	0.922	0.797	0.792	0.995	0.888	0.734	0.901	0.581	0.885	0.798	0.889	0.674	0.455	0.347	0.919	0.539	0.872	0.801	0.518	0.67
3CD	0.179	0.522	0.758	1.0	0.485	0.674	0.371	0.519	0.857	0.936	0.681	0.714	0.937	0.944	0.735	0.837	0.958	0.7	0.49	0.838	0.937	0.693	0.555	0.397	0.313	0.811	0.46	0.852	0.638	0.445	0.552
3CS	0.222	0.336	0.574	0.485	1.0	0.634	0.611	0.882	0.528	0.47	0.628	0.602	0.501	0.499	0.413	0.536	0.476	0.612	0.98	0.535	0.501	0.618	0.795	0.686	0.468	0.547	0.898	0.53	0.67	0.841	0.8
3ED	0.197	0.417	0.858	0.674	0.634	1.0	0.452	0.693	0.759	0.644	0.982	0.923	0.705	0.701	0.542	0.776	0.655	0.947	0.642	0.774	0.705	0.96	0.758	0.492	0.368	0.799	0.592	0.763	0.921	0.566	0.754
3ES	0.258	0.277	0.42	0.371	0.611	0.452	1.0	0.565	0.395	0.361	0.448	0.435	0.38	0.379	0.327	0.4	0.365	0.44	0.604	0.399	0.38	0.443	0.528	0.847	0.666	0.406	0.656	0.396	0.469	0.69	0.53
3HD	0.215	0.352	0.622	0.519	0.882	0.693	0.565	1.0	0.568	0.501	0.685	0.655	0.537	0.535	0.437	0.577	0.508	0.667	0.897	0.576	0.537	0.673	0.887	0.628	0.44	0.59	0.802	0.57	0.736	0.755	0.895
3HS	0.185	0.48	0.867	0.857	0.528	0.759	0.395	0.568	1.0	0.809	0.768	0.81	0.908	0.9	0.655	0.967	0.827	0.792	0.533	0.965	0.909	0.783	0.611	0.425	0.33	0.937	0.498	0.991	0.713	0.48	0.608
3SD	0.177	0.541	0.72	0.936	0.47	0.644	0.361	0.501	0.809	1.0	0.651	0.681	0.881	0.887	0.774	0.791	0.97	0.668	0.474	0.793	0.881	0.662	0.534	0.387	0.306	0.768	0.446	0.805	0.611	0.431	0.532
3SS	0.196	0.42	0.871	0.681	0.628	0.982	0.448	0.685	0.768	0.651	1.0	0.936	0.713	0.71	0.547	0.786	0.662	0.961	0.635	0.784	0.714	0.974	0.749	0.488	0.366	0.81	0.586	0.772	0.908	0.561	0.744
5AD	0.193	0.432	0.922	0.714	0.602	0.923	0.435	0.655	0.81	0.681	0.936	1.0	0.749	0.745	0.568	0.83	0.693	0.973	0.609	0.828	0.75	0.96	0.713	0.472	0.357	0.856	0.564	0.814	0.856	0.541	0.799
5AS	0.182	0.505	0.797	0.937	0.501	0.705	0.38	0.537	0.908	0.881	0.713	0.749	1.0	0.978	0.701	0.884	0.903	0.734	0.506	0.885	0.99	0.726	0.575	0.408	0.319	0.857	0.474	0.903	0.665	0.458	0.573
5CD	0.181	0.507	0.792	0.944	0.499	0.701	0.379	0.535	0.9	0.887	0.71	0.745	0.978	1.0	0.705	0.88	0.907	0.73	0.504	0.882	0.985	0.723	0.573	0.407	0.318	0.851	0.473	0.896	0.662	0.456	0.571
5CS	0.169	0.643	0.595	0.735	0.413	0.542	0.327	0.437	0.655	0.774	0.547	0.568	0.701	0.705	1.0	0.643	0.758	0.559	0.416	0.644	0.701	0.555	0.462	0.347	0.281	0.628	0.395	0.652	0.518	0.383	0.461
5ED	0.186	0.474	0.888	0.837	0.536	0.776	0.4	0.577	0.967	0.791	0.786	0.83	0.884	0.88	0.643	1.0	0.808	0.811	0.541	0.994	0.886	0.802	0.622	0.43	0.333	0.963	0.505	0.974	0.728	0.487	0.619
5ES	0.178	0.534	0.734	0.958	0.476	0.655	0.365	0.508	0.827	0.97	0.662	0.693	0.903	0.907	0.758	0.808	1.0	0.68	0.48	0.809	0.902	0.674	0.542	0.391	0.309	0.785	0.451	0.823	0.621	0.436	0.54
5HD	0.194	0.427	0.901	0.7	0.612	0.947	0.44	0.667	0.792	0.668	0.961	0.973	0.734	0.73	0.559	0.811	0.68	1.0	0.62	0.809	0.735	0.986	0.727	0.478	0.361	0.836	0.573	0.797	0.876	0.549	0.723
5HS	0.221	0.338	0.581	0.49	0.98	0.642	0.604	0.897	0.533	0.474	0.635	0.699	0.506	0.504	0.416	0.541	0.48	0.62	1.0	0.541	0.506	0.625	0.807	0.677	0.463	0.553	0.883	0.535	0.679	0.827	0.812
5SD	0.186	0.474	0.885	0.838	0.535	0.774	0.399	0.576	0.965	0.793	0.784	0.828	0.885	0.882	0.644	0.994	0.809	0.809	0.541	1.0	0.888	0.8	0.621	0.43	0.333	0.959	0.505	0.972	0.727	0.486	0.618
5SS	0.182	0.505	0.798	0.937	0.501	0.705	0.38	0.537	0.909	0.881	0.714	0.75	0.99	0.985	0.701	0.886	0.902	0.735	0.506	0.888	1.0	0.727	0.576	0.408	0.319	0.858	0.474	0.903	0.666	0.458	0.573
SAD	0.195	0.424	0.889	0.693	0.618	0.96	0.443	0.673	0.783	0.662	0.974	0.96	0.726	0.723	0.555	0.802	0.674	0.986	0.625	0.8	0.727	1.0	0.735	0.482	0.363	0.826	0.577	0.788	0.888	0.553	0.731
SAS	0.21	0.368	0.674	0.555	0.795	0.758	0.528	0.887	0.611	0.534	0.749	0.713	0.575	0.573	0.462	0.622	0.542	0.727	0.807	0.621	0.576	0.735	1.0	0.583	0.417	0.637	0.729	0.613	0.809	0.691	0.985
SCD	0.247	0.291	0.455	0.397	0.686	0.492	0.847	0.628	0.425	0.387	0.488	0.472	0.408	0.407	0.347	0.43	0.391	0.478	0.677	0.43	0.408	0.482	0.583	1.0	0.595	0.438	0.744	0.426	0.513	0.788	0.586
SCS	0.296	0.243	0.347	0.313	0.468	0.368	0.666	0.44	0.33	0.306	0.366	0.357	0.319	0.318	0.281	0.333	0.309	0.361	0.463	0.333	0.319	0.363	0.417	0.595	1.0	0.337	0.494	0.33	0.38	0.513	0.419
SED	0.187	0.466	0.919	0.811	0.547	0.799	0.406	0.59	0.937	0.768	0.81	0.856	0.857	0.851	0.628	0.963	0.785	0.836	0.553	0.959	0.858	0.826	0.637	0.438	0.337	1.0	0.515	0.944	0.749	0.496	0.634
SES	0.227	0.324	0.539	0.46	0.898	0.592	0.656	0.802	0.498	0.446	0.586	0.564	0.474	0.473	0.395	0.505	0.451	0.573	0.883	0.505	0.474	0.577	0.729	0.744	0.494	0.515	1.0	0.5	0.623	0.928	0.733
SHD	0.185	0.479	0.872	0.852	0.53	0.763	0.396	0.57	0.991	0.805	0.772	0.814	0.903	0.896	0.652	0.974	0.823	0.797	0.535	0.972	0.903	0.788	0.613	0.428	0.33	0.944	0.5	1.0	0.717	0.482	0.611
SHS	0.2	0.403	0.801	0.638	0.67	0.921	0.469	0.736	0.713	0.611	0.908	0.856	0.665	0.662	0.518	0.728	0.621	0.876	0.679	0.727	0.666	0.888	0.809	0.513	0.38	0.749	0.623	0.717	1.0	0.595	0.805
SSD	0.231	0.316	0.518	0.445	0.841	0.566	0.69	0.755	0.48	0.431	0.561	0.541	0.458	0.456	0.383	0.487	0.436	0.549	0.827	0.486	0.458	0.553	0.691	0.788	0.513	0.496	0.928	0.482	0.595	1.0	0.695
SSS	0.21	0.367	0.67	0.552	0.8	0.754	0.53	0.895	0.608	0.532	0.744	0.709	0.573	0.571	0.461	0.619	0.54	0.723	0.812	0.618	0.573	0.731	0.985	0.586	0.419	0.634	0.733	0.611	0.805	0.695	1.0

Table S5: Tanimoto similarity values S_T calculated with RDKit for heterodimers design with THA, THC and CBDA.

MOLECULE	THA	THC	CBDA	HC0	HC1	HC2	HC3	F	HT0	HT1	HT2	HT3
THA	1.0	0.056	0.068	0.071	0.08	0.07	0.069	0.155	0.074	0.071	0.071	0.07
THC	0.056	1.0	0.406	0.265	0.257	0.248	0.233	0.16	0.551	0.531	0.506	0.448
CBDA	0.068	0.406	1.0	0.588	0.566	0.554	0.494	0.133	0.24	0.257	0.243	0.229
HC0	0.071	0.265	0.588	1.0	0.602	0.88	0.847	0.15	0.385	0.339	0.348	0.357
HC1	0.08	0.257	0.566	0.602	1.0	0.574	0.538	0.146	0.481	0.602	0.477	0.472
HC2	0.07	0.248	0.554	0.88	0.574	1.0	0.849	0.147	0.33	0.322	0.414	0.362
HC3	0.069	0.233	0.494	0.847	0.538	0.849	1.0	0.155	0.339	0.319	0.362	0.42
F	0.155	0.16	0.133	0.15	0.146	0.147	0.155	1.0	0.172	0.187	0.185	0.184
HT0	0.074	0.551	0.24	0.385	0.481	0.33	0.339	0.172	1.0	0.819	0.854	0.821
HT1	0.071	0.531	0.257	0.339	0.602	0.322	0.319	0.187	0.819	1.0	0.802	0.753
HT2	0.071	0.506	0.243	0.348	0.477	0.414	0.362	0.185	0.854	0.802	1.0	0.847
HT3	0.07	0.448	0.229	0.357	0.472	0.362	0.42	0.184	0.821	0.753	0.847	1.0

Table S6: Inverse distance values (d^{-1}) computed by the model trained on the TKI molecules dataset, applied to the heterodimer cross-validation set.

MOLECULE	THA	THC	CBDA	HC0	HC1	HC2	HC3	F	HT0	HT1	HT2	HT3
THA	1.0	0.782	0.577	0.938	0.89	0.791	0.862	0.872	0.791	0.876	0.68	0.876
THC	0.782	1.0	0.687	0.746	0.716	0.648	0.696	0.882	0.985	0.878	0.84	0.878
CBDA	0.577	0.687	1.0	0.557	0.541	0.501	0.529	0.629	0.68	0.627	0.789	0.627
HC0	0.938	0.746	0.557	1.0	0.944	0.832	0.912	0.828	0.754	0.832	0.653	0.832
HC1	0.89	0.716	0.541	0.944	1.0	0.87	0.952	0.791	0.724	0.795	0.63	0.795
HC2	0.791	0.648	0.501	0.832	0.87	1.0	0.905	0.71	0.655	0.712	0.577	0.712
HC3	0.862	0.696	0.529	0.912	0.952	0.905	1.0	0.767	0.703	0.77	0.614	0.77
F	0.872	0.882	0.629	0.828	0.791	0.71	0.767	1.0	0.894	0.994	0.755	0.993
HT0	0.791	0.985	0.68	0.754	0.724	0.655	0.703	0.894	1.0	0.89	0.829	0.89
HT1	0.876	0.878	0.627	0.832	0.795	0.712	0.77	0.994	0.89	1.0	0.752	0.994
HT2	0.68	0.84	0.789	0.653	0.63	0.577	0.614	0.755	0.829	0.752	1.0	0.752
HT3	0.876	0.878	0.627	0.832	0.795	0.712	0.77	0.993	0.89	0.994	0.752	1.0

Table S7: Inverse distance values (d^{-1}) computed by the model trained on the AChEI inhibitor dataset, applied to the heterodimer cross-validation set

MOLECULE	THA	THC	CBDA	HC0	HC1	HC2	HC3	F	HT0	HT1	HT2	HT3
THA	1.0	0.333	0.231	0.374	0.422	0.55	0.453	0.308	0.286	0.292	0.258	0.325
THC	0.333	1.0	0.428	0.755	0.613	0.459	0.559	0.798	0.67	0.702	0.532	0.924
CBDA	0.231	0.428	1.0	0.376	0.337	0.285	0.32	0.481	0.543	0.523	0.687	0.444
HC0	0.374	0.755	0.376	1.0	0.765	0.539	0.683	0.634	0.55	0.572	0.454	0.711
HC1	0.422	0.613	0.337	0.765	1.0	0.645	0.86	0.531	0.471	0.487	0.399	0.584
HC2	0.55	0.459	0.285	0.539	0.645	1.0	0.719	0.411	0.374	0.384	0.327	0.442
HC3	0.453	0.559	0.32	0.683	0.86	0.719	1.0	0.49	0.438	0.452	0.375	0.534
F	0.308	0.798	0.481	0.634	0.531	0.411	0.49	1.0	0.806	0.854	0.615	0.854
HT0	0.286	0.67	0.543	0.55	0.471	0.374	0.438	0.806	1.0	0.935	0.722	0.708
HT1	0.292	0.702	0.523	0.572	0.487	0.384	0.452	0.854	0.935	1.0	0.688	0.745
HT2	0.258	0.532	0.687	0.454	0.399	0.327	0.375	0.615	0.722	0.688	1.0	0.557
HT3	0.325	0.924	0.444	0.711	0.584	0.442	0.534	0.854	0.708	0.745	0.557	1.0

Table S8: SMILES for TKIs data.

MOLECULE	SMILES
pona	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=C5C=CC=NN45)=C3)C</chem>
pf114	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=NN=C5C=CC=CN45)=C3)C</chem>
7a	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=4C=NC=CC4)=C3)C</chem>
7b	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=4C=NC=NC4)=C3)C</chem>
7c	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=C(C=C4)NC(=O)C)=C3)C</chem>
7d	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=C(C=C4)NC(=O)CC)=C3)C</chem>
7e	<chem>O=C(N)C1=NC=C(C#CC2=CC(=CC=C2C)C(=O)NC3=CC=C(C(=C3)C(F)(F)F)CN4CCN(C)CC4)C=C1</chem>
7f	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=C(N=C4)NC5CC5)=C3)C</chem>
8a	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=CN4)=C3)C</chem>
8b	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=CN4C)=C3)C</chem>
8c	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=C(N4C)C)=C3)C</chem>
8d	<chem>O=C(N)C1=NC=C(C#CC2=CC(=CC=C2C)C(=O)NC3=CC=C(C(=C3)C(F)(F)F)CN4CCN(C)CC4)N1C</chem>
8e	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=C(C(=O)NC)N4C)=C3)C</chem>
8f	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=CN=C(C(=O)NCCO)N4C)=C3)C</chem>
8g	<chem>O=C(N)C1=NC=C(C#CC2=CC(=CC=C2C)C(=O)NC3=CC=C(C(=C3)C(F)(F)F)CN4CCN(CCO)CC4)N1C</chem>
8h	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(CCO)CC2)C3=CC=C(C(C#CC4=CN=C(C(=O)NC)N4C)=C3)C</chem>
8i	<chem>O=C(N)C1=NC=C(C#CC2=CC(=CC=C2C)C(=O)NC3=CC=C(C(=C3)C(F)(F)F)CN4CCN(CCO)CC4)N1C</chem>
8j	<chem>O=C(N)C1=NC=C(C#CC2=CC(=CC=C2C)C(=O)NC3=CC=C(C(=C3)C(F)(F)F)CN4CCN(CC(=O)O)CC4)N1C</chem>
8k	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=4SC(=NC4)N)=C3)C</chem>
8l	<chem>O=C(NC1=CC=C(C(=C1)C(F)(F)F)CN2CCN(C)CC2)C3=CC=C(C(C#CC4=4SC(=NC4)NC(=O)C)=C3)C</chem>
2a	<chem>C(#CC1=CN=C2C=CC=NN12)C=3C=C(C=CC3C)C4=NC5=CC=C(C=C5N4)CN6CCN(C)CC6</chem>
2b	<chem>C(#CC=1C=C(C=CC1C)C2=NC3=CC(=CC=C3N2)CN4CCN(C)CC4)C5=NN=C(C=C5)NC6CCC6</chem>
2c	<chem>C(#CC=1C=C(C=CC1C)C2=NC3=CC=C(C=C3N2)CN4CCN(C)CC4)C5=NN=C(C=C5)NC6CC6</chem>
2d	<chem>C(#CC=1C=C(C=CC1C)C2=NC3=CC=C(C=C3N2)CN4CCN(C)CC4)C5=NN=C(C=C5)NC(C)C</chem>
2e	<chem>C(#CC=1C=C(C=CC1C)C2=NC3=CC=C(C=C3N2)CN4CCN(C)CC4)C5=CN=C(N=C5)NC6CC6</chem>
2f	<chem>C(#CC1=CN=C2C=CC=NN12)C=3C=C(C=CC3C)C4=NC5=CC=C(C=C5N4)N6C=NC(=C6)C</chem>
2g	<chem>ClC=1C=CC(=CC1C#CC2=CN=C3C=CC=NN23)C4=NC5=CC=C(C=C5N4)CN6CCN(C)CC6</chem>
2h	<chem>ClC=1C=CC(=CC1C#CC2=NN=C(C=C2)NC3CCC3)C4=NC5=CC(=CC=C5N4)CN6CCN(C)CC6</chem>
2i	<chem>ClC=1C=CC(=CC1C#CC2=NN=C(C=C2)NC3CCC3)C4=NC5=CC=C(C=C5N4)CN6CCN(C)CC6</chem>
2j	<chem>ClC=1C=CC(=CC1C#CC2=NN=C(C=C2)NC(C)C)C3=NC4=CC=C(C=C4N3)CN5CCN(C)CC5</chem>
2k	<chem>ClC=1C=CC(=CC1C#CC2=CN=C(N=C2)NC3CCC3)C4=NC5=CC=C(C=C5N4)CN6CCN(C)CC6</chem>

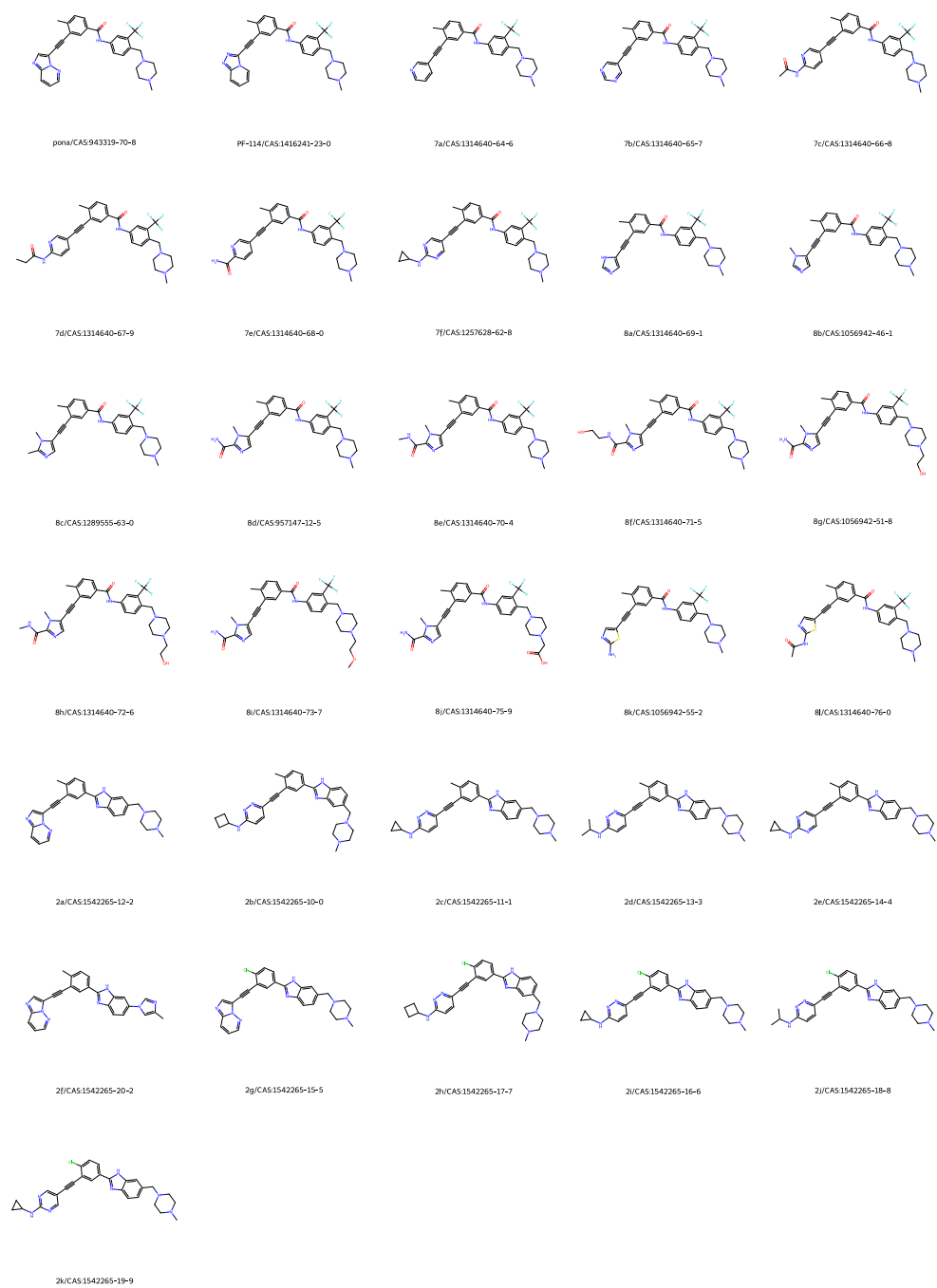


Figure S1: 2D structures for TKIs dataset.

Table S9: SMILES for AChEIs dataset.

MOLECULE	SMILES
DNP	<chem>COC1=C(C=C2C(=C1)CC(C2=O)CC3CCN(CC3)CC4=CC=CC=C4)OC</chem>
3AD	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C=C(CCC(NC3=CC([C@@H]([NH2]CC#C)CC4)=C4C=C3)=O)C2</chem>
3AS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCC(NC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C2</chem>
3CD	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C=C(CCC(C3=CC([C@H]([NH2]CC#C)CC4)=C4C=C3)=O)C2</chem>
3CS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCC(C3=CC([C@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C2</chem>
3ED	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C=C(CCCOC3=CC([C@@H]([NH2]CC#C)CC4)=C4C=C3)C2</chem>
3ES	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCOC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)C2</chem>
3HD	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C=C(CCCC3=CC([C@@H]([NH2]CC#C)CC4)=C4C=C3)C2</chem>
3HS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCCC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)C2</chem>
3SD	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C=C(CCC(OC3=CC([C@@H]([NH2]CC#C)CC4)=C4C=C3)=O)C2</chem>
3SS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCC(OC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C2</chem>
5AD	<chem>OCCCC1=C[C@H]2CC(C1)C=C(CCCCC(NC3=CC=C4C([C@@H]([NH2+]CC#C)CC4)=C3)=O)C2</chem>
5AS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCCC(NC3=CC=C4C([C@@H]([NH2+]CC#C)CC4)=C3)=O)C2</chem>
5CD	<chem>OCCCC1=C[C@H]2CC(C1)C=C(CCCCC(C3=CC=C(CC[C@H]4[NH2+]CC#C)C4=C3)=O)C2</chem>
5CS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCCC(C3=CC=C(CC[C@H]4[NH2+]CC#C)C4=C3)=O)C2</chem>
5ED	<chem>OCCCC1=C[C@H]2CC(C1)C=C(CCCCCOC3=CC=C4C([C@@H]([NH2+]CC#C)CC4)=C3)C2</chem>
5ES	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCCCOC3=CC=C4C([C@@H]([NH2+]CC#C)CC4)=C3)C2</chem>
5HD	<chem>OCCCC1=C[C@H]2CC(C1)C=C(CCCCCC3=CC=C(CC[C@H]4[NH2+]CC#C)C4=C3)C2</chem>
5HS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCCCC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)C2</chem>
5SD	<chem>OCCCC1=C[C@H]2CC(C1)C=C(CCCCC(OC3=CC=C4C([C@@H]([NH2+]CC#C)CC4)=C3)=O)C2</chem>
5SS	<chem>OCCCC1=C[C@H]2C[C@@H](C1)C[C@H](CCCC(OC3=CC=C4C([C@@H]([NH2+]CC#C)CC4)=C3)=O)C2</chem>
SAD	<chem>OCCCC1=C[C@@H]2C(CCC(NC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C[C@H]1C2</chem>
SAS	<chem>OCCCC1=C[C@H]2[C@@H](CCC(NC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C[C@@H]1C2</chem>
SCD	<chem>OCCCC1=C[C@@H]2C(CCC(C3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C[C@H]1C2</chem>
SCS	<chem>OCCCC1=C[C@H]2[C@@H](CCC(C3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C[C@@H]1C2</chem>
SED	<chem>OCCCC1=C[C@@H]2C(CCC(OC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)=O)C[C@H]1C2</chem>
SES	<chem>OCCCC1=C[C@@H]2[C@@H](CCOC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)C[C@H]1C2</chem>
SHD	<chem>OCCCC1=C[C@H]2C(CCCC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)C[C@@H]1C2</chem>
SHS	<chem>OCCCC1=C[C@@H]2[C@@H](CCCC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)C[C@H]1C2</chem>
SSD	<chem>OCCCC1=C[C@H]2C(CCCOC3=CC([C@@H]([NH2+]CC#C)CC4)=C4C=C3)C[C@@H]1C2</chem>
SSS	<chem>OCCCC1=C[C@H]2[C@H](C[C@@H]1C2)CCC(OC3=CC4=C(C=C3)CC[C@@H]4[NH2+]CC#C)=O</chem>

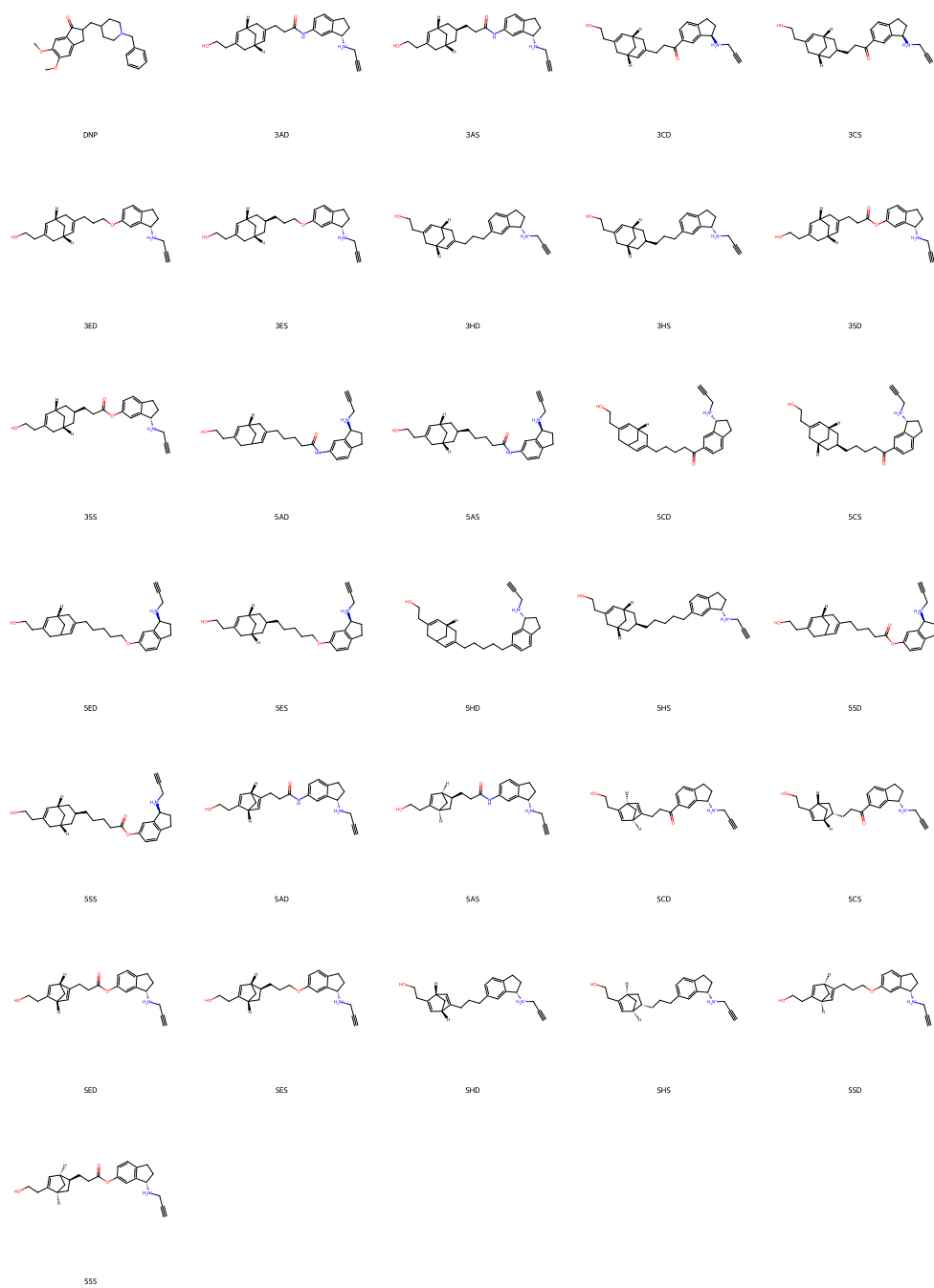


Figure S2: 2D structures for AChEIs based huprine-ladostigil heterodimers dataset.

Table S10: SMILES of potential heterodimers AChEIs dataset.

MOLECULE	SMILES
THA	<chem>NC1=C2CCCCC2=NC2=CC=CC=C12</chem>
THC	<chem>[H][C@@]12C=C(C)CC[C@@]1([H])C(C)(C)OC1=C2C(O)=CC(CCCCC)=C1</chem>
CBDA	<chem>Oc1c([C@H]2[C@@H](CCC(=C2)C)C(=C)C)c(O)cc(c1C(=O)O)CCCC</chem>
CBDA0	<chem>CC(=C)[C@@H]1CCC(C)=C[C@H]1c1c(O)cc(CCCCCNC2=C3CC=CC=C3NC3=C2CCCC3)c(C(O)=O)c1O</chem>
CBDA1	<chem>CC(=C)[C@@H]1CCC(C)=C[C@H]1c1c(O)cc(CCCCC(=O)NC2=C3C=CC=CC3NC3=C2CCCC3)c(C(O)=O)c1O</chem>
CBDA2	<chem>CC(=C)[C@@H]1CCC(C)=C[C@H]1c1c(O)cc(CCCC(=O)CCNC2=C3CC=CC=C3NC3=C2CCCC3)c(C(O)=O)c1O</chem>
CBDA3	<chem>CC(=C)[C@@H]1CCC(C)=C[C@H]1c1c(O)cc(CC(=O)CCCCNC2=C3CC=CC=C3NC3=C2CCCC3)c(C(O)=O)c1O</chem>
F	<chem>CC1=C2CCC=C[C@H]2c2ccc(CCNC(=O)CC3=C4C=CC=CC4=[NH+][C4=C3CCCC4)cc2O1</chem>
THC0	<chem>CC1=C[C@@H]2[C@@H](CC1)C(C)(C)Oc1cc(CCCCCNC3=C4C=CC=CC4NC4=C3CCCC4)cc(O)c21</chem>
THC1	<chem>CC1=C[C@@H]2[C@@H](CC1)C(C)(C)Oc1cc(CCCCC(=O)NC3=C4C=CC=CC4NC4=C3CCCC4)cc(O)c21</chem>
THC2	<chem>CC1=C[C@@H]2[C@@H](CC1)C(C)(C)Oc1cc(CCCC(=O)CCNC3=C4C=CC=CC4NC4=C3CCCC4)cc(O)c21</chem>
THC3	<chem>CC1=C[C@@H]2[C@@H](CC1)C(C)(C)Oc1cc(CC(=O)CCCCNC3=C4C=CC=CC4NC4=C3CCCC4)cc(O)c21</chem>

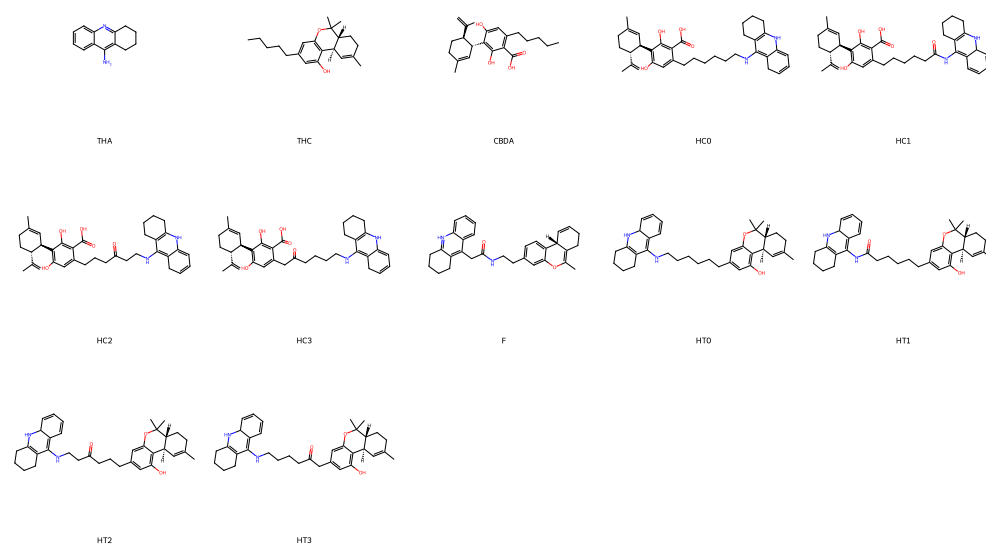


Figure S3: 2D structures for AChEIs based tacrine-thc-cbda heterodimers dataset.

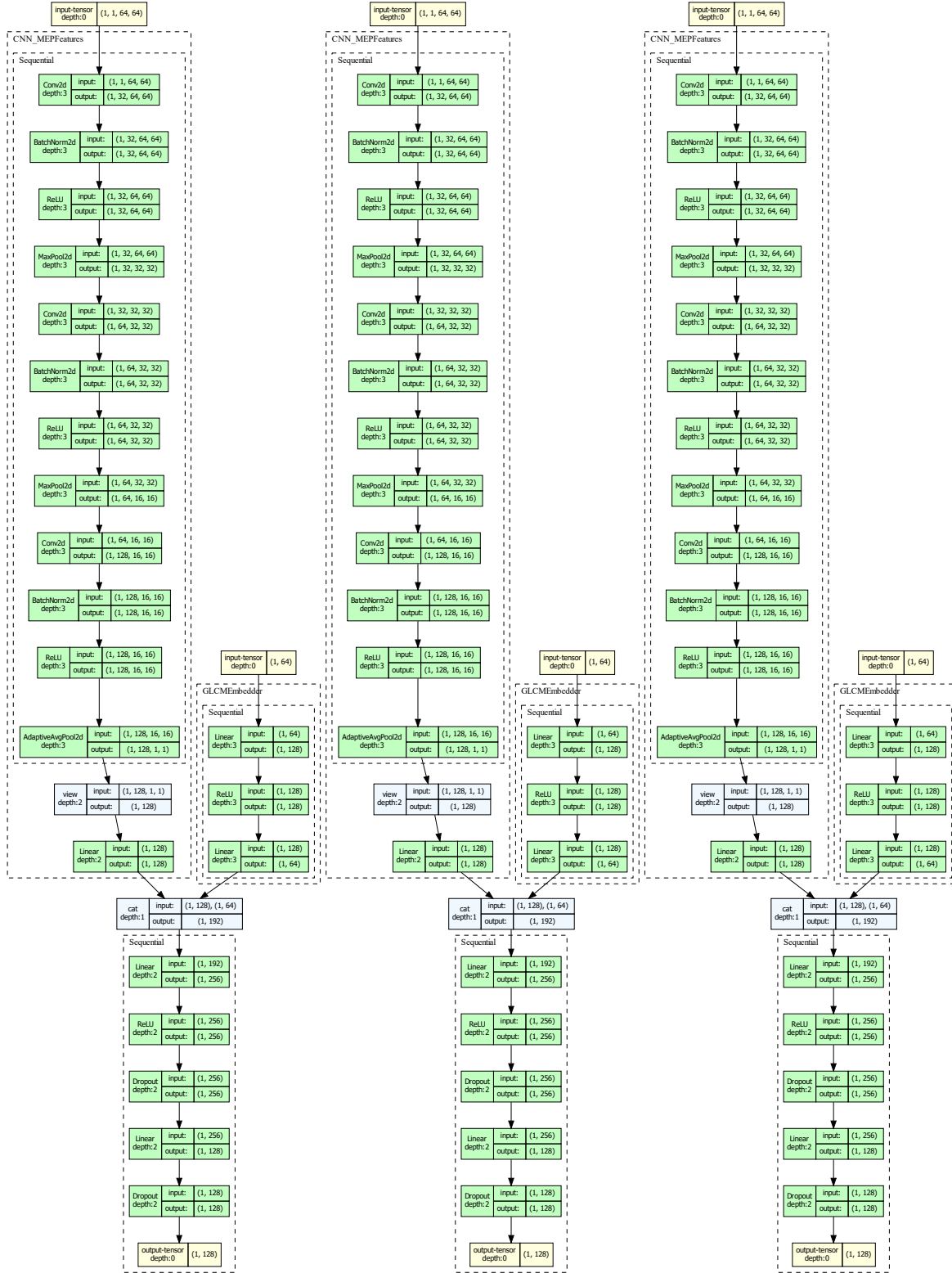


Figure S4: Architecture of the developed model

Architecture and Implementation Details

The model architecture receives an input set $\mathbf{X}_{MEP} \subseteq \mathbb{R}^{1 \times \text{height} \times \text{width}}$ for the MEP images, and $\mathbf{X}_{glcm} \leftarrow rdg \subseteq \mathbb{R}^{d_t}$ for the GLCM matrices generated from the corresponding RDG diagram images, with $d_t = 64$, given that the GLCM matrices were defined with 8 levels (8 x 8). The model architecture is divided into three parts; the first extracts visual information from the MEP images.

$$f_{\text{cnn}} : \mathbf{X}_{MEP} \rightarrow \mathbb{R}^{d_c}, f_{\text{cnn}}(\mathbf{x}_{MEP}) = \mathbf{W}_c \cdot \text{Flatten}(\text{CNN}(\mathbf{x}_{MEP})) + b_c \quad (1)$$

Where $d_c = 128$ is the dimension, $\mathbf{W}_c$ is the weight vector of the last linear layer of the CNN submodel, which consists of three blocks of Conv2D + ReLU + Pooling + AdaptiveAvgPool (further details in Figure 4 in the supplementary material), and b_c is the bias of the last linear layer.

The second part of the model consists of a multilayer perceptron (MLP) with two linear layers, which learns texture information from the RDG diagrams corresponding to the MEP images, using the GLCM co-occurrence matrix as input.

$$f_{\text{mlp}} : \mathbf{X}_{glcm \leftarrow rdg} \rightarrow \mathbb{R}^{d_t}, f_{\text{mlp}}(\mathbf{x}_{glcm \leftarrow rdg}) = \mathbf{W}_2 \cdot (\text{ReLU}(\mathbf{W}_1 \cdot \mathbf{x}_{glcm \leftarrow rdg} + b_1)) + b_2 \quad (2)$$

Where $d_t = 64$, $\mathbf{W}_1 \in \mathbb{R}^{128 \times 64}$ and $\mathbf{W}_2 \in \mathbb{R}^{64 \times 128}$. The third part of the model is a multimodal projector that combines the visual representations learned by the CNN in the first part with the texture features extracted by the MLP in the second part into a shared embedding space $\mathbb{R}^{d_e}$ with $d_e = 128$.

$$\phi : \mathbb{R}^{d_\nu} \rightarrow \mathbb{R}^{d_e}, \phi(\nu) = \text{Dropout}(\mathbf{W}_4 \cdot \text{Dropout}(\text{ReLU}(\mathbf{W}_3 \cdot \nu + b_3))) + b_4 \quad (3)$$

Where $\mathbf{W}_3 \in \mathbb{R}^{128 \times 192}$, $\mathbf{W}_4 \in \mathbb{R}^{128 \times 128}$ and $d_\nu = 192$ is the concatenated dimension resulting from d_c and d_t , ν is the vector in the concatenated space, and the dropout prob-

ability is set to 0.3 for the *Dropout()* function. Therefore, the global embedding function $\Phi(\mathbf{x}_{\text{MEP}}, \mathbf{x}_{\text{glcm} \leftarrow \text{rdg}})$ can be defined as

$$\Phi : \mathbb{R}^{\text{dc}} \times \mathbb{R}^{\text{dt}} \rightarrow \mathbb{R}^{\text{de}}, \quad \Phi(\mathbf{x}_{\text{MEP}}, \mathbf{x}_{\text{glcm} \leftarrow \text{rdg}}) = \phi([f_{\text{cnn}}(\mathbf{x}_{\text{MEP}}); f_{\text{glcm} \leftarrow \text{rdg}}(\mathbf{x}_{\text{glcm} \leftarrow \text{rdg}})]) \quad (4)$$

The cost function that the model aims to maximize is the triplet loss, as it is a Siamese network designed to learn similarity and dissimilarity between images.

$$\mathcal{L} = \max(0, \|\Phi(\mathbf{a}_{\text{MEP}}, \mathbf{a}_{\text{glcm} \leftarrow \text{rdg}}) - \Phi(\mathbf{p}_{\text{MEP}}, \mathbf{p}_{\text{glcm} \leftarrow \text{rdg}})\|_2^2 - \|\Phi(\mathbf{a}_{\text{MEP}}, \mathbf{a}_{\text{glcm} \leftarrow \text{rdg}}) - \Phi(\mathbf{n}_{\text{MEP}}, \mathbf{n}_{\text{glcm} \leftarrow \text{rdg}})\|_2^2 + \alpha) \quad (5)$$

Where α is the margin that defines the minimum distance between the positive and negative pair distances, $\mathbf{a}_{\text{MEP}}$ and $\mathbf{a}_{\text{glcm} \leftarrow \text{rdg}}$ are the anchor values, $\mathbf{p}_{\text{MEP}}$ and $\mathbf{p}_{\text{glcm} \leftarrow \text{rdg}}$ correspond to the positive samples (similar images), and $\mathbf{n}_{\text{MEP}}$ and $\mathbf{n}_{\text{glcm} \leftarrow \text{rdg}}$ correspond to the negative samples (images dissimilar to the anchor). Finally, $\|\cdot\|_2$ denotes the Euclidean distance (L2 norm). The algorithm below presents the developed method using simplified mathematical notation.

Algorithm: Training of the Siamese Network for Molecular Similarity via MEP and GLCM

Require: Set of MEP images and GLCM vectors, similarity matrix S_T , margin α , number of epochs E , and model Φ

Initialize CNN, MLP, and the multimodal projector of Φ

for $e = 1$ **to** E **do**

▷ For each epoch

 Build triplets $(\mathbf{a}, \mathbf{p}, \mathbf{n})$ such that:

$S_T(\mathbf{a}, \mathbf{p}) \geq 0.70$ (positive) and $S_T(\mathbf{a}, \mathbf{n}) \leq 0.40$ (negative)

▷ Or another criterion

for each triplet $(\mathbf{a}, \mathbf{p}, \mathbf{n})$ **do**

$\mathbf{z}_a \leftarrow \Phi(\mathbf{a}_{\text{MEP}}, \mathbf{a}_{\text{glcm}})$

$\mathbf{z}_p \leftarrow \Phi(\mathbf{p}_{\text{MEP}}, \mathbf{p}_{\text{glcm}})$

$\mathbf{z}_n \leftarrow \Phi(\mathbf{n}_{\text{MEP}}, \mathbf{n}_{\text{glcm}})$

 Compute loss:

$\mathcal{L} \leftarrow \max(0, \|\mathbf{z}_a - \mathbf{z}_p\|^2 - \|\mathbf{z}_a - \mathbf{z}_n\|^2 + \alpha)$

 Update weights via backpropagation using $\mathcal{L}$

end for

end for

return Φ
